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PROFESSIONAL INFORMATION BROCHURE

ARIMIDEX®

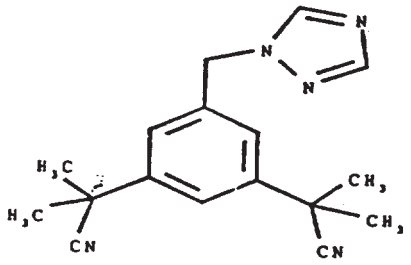
(anastrozole) Tablets

~~Rev F 07/98~~
Rev H-6 05/00

~~64076-04~~
SIC No. XXXXX-XX

DESCRIPTION

ARIMIDEX® (anastrozole) tablets for oral administration contain 1 mg of anastrozole, a non-steroidal aromatase inhibitor. It is chemically described as 1,3-Benzenediacetonitrile, α, α, α', α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Its molecular formula is $C_{17}H_{19}N_5$ and its structural formula is:



Anastrozole is an off-white powder with a molecular weight of 293.4. Anastrozole has moderate aqueous solubility (0.5 mg/mL at 25°C); solubility is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and very soluble in acetonitrile.

Each tablet contains as inactive ingredients: lactose, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, povidone, sodium starch glycolate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by estrogen. In post-menopausal women, the principal source of circulating estrogen (primarily estradiol) is conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissues, such as adipose tissue, with further conversion of estrone to estradiol. Many breast cancers also contain aromatase; the importance of tumor-generated estrogens is uncertain.

Treatment of breast cancer has included efforts to decrease estrogen levels, by ovariectomy premenopausally and by use of anti-estrogens and progestational agents both pre- and post-menopausally; and these interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.

Anastrozole is a potent and selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteriods or aldosterone.

Pharmacokinetics

Inhibition of aromatase activity is primarily due to anastrozole, the parent drug. Studies with radiolabeled drug have demonstrated that orally administered anastrozole is well absorbed into the systemic circulation with 83 to 85% of the radiolabel recovered in urine and feces. Food does not affect the extent of absorption. Elimination of anastrozole is primarily via hepatic metabolism (approximately 85%) and to a lesser extent, renal excretion (approximately 11%), and anastrozole has a mean terminal elimination half-life of approximately 50 hours in postmenopausal women. The major circulating metabolite of anastrozole, triazole, lacks pharmacologic activity. The pharmacokinetic parameters are similar in patients and in healthy postmenopausal volunteers. The pharmacokinetics of anastrozole are linear over the dose range of 1 to 20 mg and do not change with repeated dosing. Consistent with the approximately 2-day terminal elimination half-life, plasma concentrations approach steady-state levels at about 7 days of once daily dosing and steady-state levels are approximately three- to four-fold higher than levels observed after a single dose of ARIMIDEX. Anastrozole is 40% bound to plasma proteins in the therapeutic range.

Metabolism and Excretion: Studies in postmenopausal women demonstrated that anastrozole is extensively metabolized with about 10% of the dose excreted in the urine as unchanged drug within 72 hours of dosing, and the remainder (about 60% of the dose) is excreted in urine as metabolites. Metabolism of anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. Three metabolites of anastrozole have been identified in human plasma and urine. The known metabolites are triazole, a glucuronide conjugate of hydroxy-anastrozole, and a glucuronide of anastrozole itself. Several minor (less than 5% of the radioactive dose) metabolites have not been identified.

Because renal elimination is not a significant pathway of elimination, total body clearance of anastrozole is unchanged even in severe (creatinine clearance less than 30 mL/min/1.73m^2) renal impairment, dosing adjustment in patients with renal dysfunction is not necessary (see Special Populations and DOSAGE AND ADMINISTRATION sections). Dosage adjustment is also unnecessary in patients with stable hepatic cirrhosis (see Special Populations and DOSAGE AND ADMINISTRATION sections).

Special Populations:

Geriatric: Anastrozole pharmacokinetics have been investigated in postmenopausal female volunteers and patients with breast cancer. No age related effects were seen over the range <50 to >80 years.

Race: Estradiol and estrone sulfate levels were similar between Japanese and Caucasian post-menopausal women who received 1 mg of anastrozole daily for 16 days. Anastrozole mean steady state minimum plasma concentrations in Caucasian and Japanese post-menopausal women were 25.7 and 30.4 ng/mL respectively.

Renal Insufficiency: Anastrozole pharmacokinetics have been investigated in subjects with renal insufficiency. Anastrozole renal clearance decreased proportionally with creatinine clearance and was approximately 50% lower in volunteers with severe renal impairment (creatinine clearance < 30 mL/min/1.73m^2) compared to controls. Since only about 10% of anastrozole is excreted unchanged in the urine, the reduction in renal clearance did not influence the total body clearance. (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Anastrozole pharmacokinetics have been investigated in subjects with hepatic cirrhosis related to alcohol abuse. The apparent oral clearance (CL/F) of anastrozole was approximately 30% lower in subjects with stable hepatic cirrhosis than in control subjects with normal liver function. However, plasma anastrozole concentrations in the subjects with hepatic cirrhosis were within the range of concentrations seen in normal subjects across all clinical trials (see DOSAGE AND ADMINISTRATION), so that no dosage adjustment is needed.

Drug-Drug Interactions: Anastrozole inhibited reactions catalyzed by cytochrome P450 1A2, 2C8/9, and 3A4 *in vitro* with Ki values which were approximately 30 times higher than the mean steady-state C_{max} values observed following a 1 mg daily dose. Anastrozole had no inhibitory effect on reactions catalyzed by cytochrome P450 2A6 or 2D6 *in vitro*. Administration of a single 30 mg/kg or multiple 10 mg/kg doses of anastrozole to subjects had no effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. Based on these *in vitro* and *in vivo* results, it is unlikely that co-administration of ARIMIDEX 1 mg with other drugs will result in clinically significant inhibition of cytochrome P450 mediated metabolism.

In a study conducted in 16 male volunteers, anastrozole did not alter the pharmacokinetics as measured by C_{max} and AUC, and anticoagulant activity as measured by prothrombin time, activated partial thromboplastin time, and thrombin time of both R- and S-warfarin.

Pharmacodynamics

Effect on Estradiol: Mean serum concentrations of estradiol were evaluated in multiple daily dosing trials with 0.5, 1, 3, 5, and 10 mg of ARIMIDEX in postmenopausal women with advanced breast cancer. Clinically significant suppression of serum estradiol was seen with all doses. Doses of 1 mg and higher resulted in suppression of mean serum concentrations of estradiol to the lower limit of detection (3.7 pmol/L). The recommended daily dose, ARIMIDEX 1 mg, reduced estradiol by approximately 70% within 24 hours and by approximately 80% after 14 days of daily dosing. Suppression of serum estradiol was maintained for up to 6 days after cessation of daily dosing with ARIMIDEX 1 mg.

Effect on Corticosteroids: In multiple daily dosing trials with 3, 5, and 10 mg, the selectivity of anastrozole was assessed by examining effects on corticosteriod synthesis. For all doses, anastrozole did not affect cortisol or aldosterone secretion at baseline or in response to ACTH. No glucocorticoid or mineralcorticoid replacement therapy is necessary with anastrozole.

Other Endocrine Effects: In multiple daily dosing trials with 5 and 10 mg, thyroid stimulating hormone (TSH) was measured; there was no increase in TSH during the administration of ARIMIDEX. ARIMIDEX does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

Clinical Studies - First Line Therapy in Postmenopausal Women with Advanced Breast Cancer: Two double-blind well-controlled clinical studies of similar design (0030, a North American study and 0027, a predominately European study) were conducted to assess the efficacy of ARIMIDEX compared with tamoxifen as first-line therapy for hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer in postmenopausal women. A total of 1021 patients between the ages of 30 and 92 years old were randomized to receive trial treatment. Patients were randomized to receive 1 mg of ARIMIDEX once daily or 20 mg of tamoxifen once daily. The primary end points for both trials were time to tumor progression, objective tumor response rate, and safety.

Demographics and other baseline characteristics, including patients who had measurable and no measurable disease, patients who were given previous adjuvant therapy, the site of metastatic disease and ethnic origin were similar for the two treatment groups for both trials. The following table summarizes the hormone receptor status at entry for all randomized patients in trials 0030 and 0027.

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